

Express Mail mailing label number: EV 325427124 US

Date of Deposit: 29 September 2003

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SPECIFICATION

TO ALL WHOM IT MAY CONCERN:

I, Michael Fantuzzi, a resident of Glendale, California, and a Citizen of the United States of America, have invented certain new and useful improvements in a

SOLUBILIZED CoQ-10

of which the following is a specification.

SOLUBILIZED CoQ-10

CROSS-REFERENCE TO RELATED APPLICATION(S)

[001] None.

FIELD OF THE INVENTION

5 **[002]** The present invention relates to the solubilization of coenzyme Q-10 and analogs thereof in monoterpenes, thereby providing increased bioavailability in delivery.

BACKGROUND OF THE INVENTION

10 **[003]** CoQ-10 (coenzyme Q10) is a fat-soluble quinone that is structurally similar to vitamin K and commonly known as ubiquinone. CoQ-10 is found in most living organisms, and is essential for the production of cellular energy. CoQ-10 (2,3 dimethyl-5 methyl-6-decaprenyl benzoquinone) is an endogenous antioxidant found in small amounts in meats and seafood. Although CoQ-10 is found in all human cells, the highest concentrations of CoQ-10 occur
15 in the heart, liver, kidneys, and pancreas. It is found naturally in the organs of many mammalian species.

[004] CoQ-10 can be synthesized in the body or it can be derived from dietary sources. Situations may arise, however, when the need for CoQ-10 surpasses the body's ability to synthesize it. CoQ-10 can be absorbed by oral
20 supplementation as evidenced by significant increases in serum CoQ-10 levels after supplementation.

[005] CoQ-10 is an important nutrient because it lies within the membrane of a cell organelle called the mitochondria. Mitochondria are known as the "power house" of the cell because of their ability to produce cellular
25 energy, or ATP, by shuttling protons derived from nutrient breakdown through the process of aerobic (oxygen) metabolism. CoQ-10 also has a secondary role as an antioxidant. CoQ-10, due to the involvement in ATP synthesis, affects the

function of almost all cells in the body, making it essential for the health of all human tissues and organs. CoQ-10 particularly effects the cells that are the most metabolically active: heart, immune system, gingiva, and gastric mucosa

5 [006] Several clinical trials have shown CoQ-10 to be effective in supporting blood pressure and cholesterol levels. Furthermore, CoQ-10 has also been shown to improve cardiovascular health. CoQ-10 has been implicated as being an essential component in thwarting various diseases such as certain types of cancers. These facts lead many to believe that CoQ-10 supplementation is vital to an individual's well being.

10 [007] CoQ-10 is sparingly soluble in most hydrophilic solvents such as water. Therefore, CoQ-10 is often administered in a powdered form, as in a tablet or as a suspension. However, delivery of CoQ-10 by these methods limits the bioavailability of the material to the individual.

15 [008] There is a need in the art for an improved methodology to deliver increased amount of bioavailable CoQ-10 to an individual in need thereof.

BRIEF SUMMARY OF THE INVENTION

20 [009] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) can be readily dissolved in varying concentrations in monoterpenes. Generally, until the present discovery, most CoQ-10 liquid delivery methods could solubilize only up to about 5% by weight of the CoQ-10 in the "solvent". Typical solvents included various oils or the CoQ-10 was held in suspension. The present invention provides the ability to solubilize CoQ-10 in monoterpenes in concentrations of up to about 60% (weight to weight) without the need to aggressively heat the solution or with gentle warming. In particular, 25 the solubilization of the CoQ-10 with monoterpenes can be accomplished at ambient temperatures.

[010] In one aspect, the present invention pertains to compositions that include coenzyme Q-10 or an analog thereof with a sufficient quantity of a monoterpene that is suitable to solubilize said coenzyme Q-10 and a

pharmaceutically acceptable carrier. Generally, about 30 to about 45% of the CoQ-10 (by weight) is solubilized in the monoterpene. In particular, the monoterpene is limonene. The compositions of the invention are useful as dietary supplements or as nutraceuticals.

5 [011] In particular, the compositions of the invention are included in a soft gelatin (soft gel) capsule. Typically, the soft gelatin capsule includes at least 5% by weight of coenzyme Q-10 or an analog thereof solubilized in a monoterpene. Typical monoterpenes include, for example, perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of
10 perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

[012] In another embodiment, the present invention pertains to methods for delivery of an effective amount of bioavailable CoQ-10 to an individual. The method includes providing CoQ-10 solubilized in a monoterpene, such that an
15 effective amount of CoQ-10 is provided to the individual.

[013] In still another embodiment, the present invention also includes packaged formulations of the invention that include a monoterpene as a solvent for the CoQ-10 and instructions for use of the tablet, capsule, elixir, etc.

20 [014] While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the invention. As will be realized, the invention is capable of modifications in various obvious aspects, all without departing from the spirit and scope of the present invention. Accordingly, the drawings and detailed
25 description are to be regarded as illustrative in nature and not restrictive.

DETAILED DESCRIPTION

[015] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) can be readily dissolved in varying concentrations in monoterpenes. CoQ-10 is found in most living organisms, and is essential for the

production of cellular energy. Ubiquinone is a naturally occurring hydrogen carrier in the respiratory chain (coenzyme Q) and structurally, it is a 2,3-dimethoxy-5-methyl-1,4-benzoquinone with a multiprenyl side chain, the number of isoprene units varying depending upon the organism from which it is derived. CoQ-10 analogs include reduced and semi-reduced CoQ-10 and ubiquinone derivatives described, for example, in WO 8803015, the teachings of which are incorporated herein by reference.

[016] Generally, until the present discovery, most CoQ-10 liquid delivery methods could solubilize only up at most about 10% by weight of the CoQ-10 in the "solvent. Typical solvents included oils or the CoQ-10 was held in an aqueous suspension. Alternatively, the CoQ-10 was provided as a solid in a tablet or powder.

[017] The present invention provides the ability to solubilize CoQ-10 in monoterpenes, as defined herein, in concentrations of up to about 60% (weight to weight) without the need to heat the solution. In one aspect, the monoterpene solubilizes CoQ-10 from about 0.1 percent by weight to about 45 percent by weight.

[018] In particular, the solubilization of the CoQ-10 with monoterpenes can be accomplished at ambient temperatures. In one aspect, from about 5 to about 50 percent (weight CoQ-10/weight solvent) CoQ-10 can be solubilized in a monoterpene. In another aspect, from about 15 to about 40 percent w/w can be solubilized and in still another aspect, from about 20 to about 35 percent w/w CoQ-10 can be solubilized in a monoterpene.

[019] The phrase "sufficient quantity of a monoterpene suitable to solubilize coenzyme Q-10" is therefore intended to mean that that amount of a monoterpene that will dissolve CoQ-10 under a given set of conditions, generally, those at ambient temperature. This determination should be understood by one skilled in the art and can be determined by methods known in the art, such as by solubility studies.

[020] One of the particular advantages of utilizing monoterpenes in combination with CoQ-10 is that the enzyme is dissolved by the monoterpene. That is, many formulations currently in the marketplace have CoQ-10 present as a suspension; a situation where not all the CoQ-10 is dissolved. This reduces efficacy and the bioavailability of the CoQ-10. The present invention eliminates this disadvantage by solubilizing the CoQ-10 in the monoterpene.

[021] A particular advantage in using monoterpenes is that the CoQ-10 does not have to be heated to dissolve into solution. This is important so that the CoQ-10 does not degrade upon dissolution.

[022] The term "monoterpene" as used herein, refers to a compound having a 10-carbon skeleton with non-linear branches. A monoterpene refers to a compound with two isoprene units connected in a head-to-end manner. The term "monoterpene" is also intended to include "monoterpenoid", which refers to a monoterpene-like substance and may be used loosely herein to refer collectively to monoterpenoid derivatives as well as monoterpenoid analogs. Monoterpenoids can therefore include monoterpenes, alcohols, ketones, aldehydes, ethers, acids, hydrocarbons without an oxygen functional group, and so forth.

[023] It is common practice to refer to certain phenolic compounds, such as eugenol, thymol and carvacrol, as monoterpenoids because their function is essentially the same as a monoterpenoid. However, these compounds are not technically "monoterpenoids" (or "monoterpenes") because they are not synthesized by the same isoprene biosynthesis pathway, but rather by production of phenols from tyrosine. However, common practice will be followed herein. Suitable examples of monoterpenes include, but are not limited to, limonene, pinene, citronellol, terpinene, nerol, menthane, carveol, S-linalool, safrol, cinnamic acid, apiol, geraniol, thymol, citral, carvone, camphor, etc. and derivatives thereof. For information about the structure and synthesis of terpenes, including terpenes of the invention, see Kirk-Othmer Encyclopedia of Chemical

Technology, Mark, et al., eds., 22:709-762 3d Ed (1983), the teachings of which are incorporated herein in their entirety.

5 [024] In particular, suitable limonene derivatives include perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

10 [025] Formulation of the CoQ-10 can be accomplished by many methods known in the art. For example, the solubilized CoQ-10 can be formulated in a suspension, an emulsion, an elixir, a solution, a caplet that harbors the liquid, or in a soft gelatin capsule. Often the formulation will include an acceptable carrier, such as an oil, or other suspending agent.

15 [026] Suitable carriers include but are not limited to, for example, fatty acids, esters and salts thereof, that can be derived from any source, including, without limitation, natural or synthetic oils, fats, waxes or combinations thereof. Moreover, the fatty acids can be derived, without limitation, from non-hydrogenated oils, partially hydrogenated oils, fully hydrogenated oils or combinations thereof. Non-limiting exemplary sources of fatty acids (their esters and salts) include seed oil, fish or marine oil, canola oil, vegetable oil, safflower oil, sunflower oil, nasturtium seed oil, mustard seed oil, olive oil, sesame oil, soybean oil, corn oil, peanut oil, cottonseed oil, rice bran oil, babassu nut oil, 20 palm oil, low erucic rapeseed oil, palm kernel oil, lupin oil, coconut oil, flaxseed oil, evening primrose oil, jojoba, tallow, beef tallow, butter, chicken fat, lard, dairy butterfat, shea butter or combinations thereof.

25 [027] Specific non-limiting exemplary fish or marine oil sources include shellfish oil, tuna oil, mackerel oil, salmon oil, menhaden, anchovy, herring, trout, sardines or combinations thereof. In particular, the source of the fatty acids is fish or marine oil (DHA or EPA), soybean oil or flaxseed oil. Alternatively or in combination with one of the above identified carrier, beeswax can be used as a suitable carrier, as well as suspending agents such as silica (silicon dioxide).

[028] The formulations of the invention are considered dietary supplements useful to the increase the amounts of CoQ-10 in the individuals in need thereof.

5 **[029]** Alternatively, the formulations of the invention are also considered to be nutraceuticals. The term "nutraceutical" is recognized in the art and is intended to describe specific chemical compounds found in foods that may prevent disease. CoQ-10 is one such compound.

10 **[030]** The formulations of the invention can further include various ingredients to help stabilize, or help promote the bioavailability of the CoQ-10, or serve as additional nutrients to an individual's diet. Suitable additives can include vitamins and biologically-acceptable minerals. Non-limiting examples of vitamins include vitamin A, B vitamins, vitamin C, vitamin D, vitamin E, vitamin K and folic acid. Non-limiting examples of minerals include iron, calcium, magnesium, potassium, copper, chromium, zinc, molybdenum, iodine, boron, selenium, manganese, derivatives thereof or combinations thereof. These
15 vitamins and minerals may be from any source or combination of sources, without limitation. Non-limiting exemplary B vitamins include, without limitation, thiamine, niacinamide, pyridoxine, riboflavin, cyanocobalamin, biotin, pantothenic acid or combinations thereof.

20 **[031]** Vitamin(s), if present, are present in the composition of the invention in an amount ranging from about 5 mg to about 500 mg. More particularly, the vitamin(s) is present in an amount ranging from about 10 mg to about 400 mg. Even more specifically, the vitamin(s) is present from about 250 mg to about 400 mg. Most specifically, the vitamin(s) is present in an amount
25 ranging from about 10 mg to about 50 mg. For example, B vitamins are in usually incorporated in the range of about 1 milligram to about 10 milligrams, i.e., from about 3 micrograms to about 50 micrograms of B12. Folic acid, for example, is generally incorporated in a range of about 50 to about 400 micrograms, biotin is generally incorporated in a range of about 25 to about 700

micrograms and cyanocobalamin is incorporated in a range of about 3 micrograms to about 50 micrograms.

5 [032] Mineral(s), if present, are present in the composition of the invention in an amount ranging from about 25 mg to about 1000 mg. More particularly, the mineral(s) are present in the composition ranging from about 25 mg to about 500 mg. Even more particularly, the mineral(s) are present in the composition in an amount ranging from about 100 mg to about 600 mg.

10 [033] Various additives can be incorporated into the present compositions. Optional additives of the present composition include, without limitation, phospholipids, L-carnitine, starches, sugars, fats, antioxidants, amino acids, proteins, flavorings, coloring agents, hydrolyzed starch(es) and derivatives thereof or combinations thereof.

15 [034] As used herein, the term "phospholipid" is recognized in the art, and refers to phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl serine, phosphatidyl choline, phosphatidyl ethanolamine, as well as phosphatidic acids, ceramides, cerebroside, sphingomyelins and cardiolipins.

20 [035] L-carnitine is recognized in the art and facilitates transport of materials through the mitochondrial membrane. L-carnitine is an essential fatty acid metabolism cofactor that helps to move fatty acids to the mitochondria from the cytoplasm. This is an important factor as this is where CoQ-10 uptake occurs.

25 [036] In one aspect of the present invention, L-carnitine is included in soft gel formulations in combination with CoQ-10. Suitable ratios of L-carnitine and CoQ-10 are known in the art and include those described in US Patent No. 4,599,232, issued to Sigma Tau Industrie Farmaceutiche Riunite S.p.A. on July 8, 1986, the teachings of which are incorporated herein in their entirety. In particular, combinations of limonene, CoQ-10 and L-carnitine in soft gel formulations are of importance. The present invention provides the advantage of solvating large amounts (relative to that of current state of the art) of CoQ-10 in limonene in a soft gel capsule along with an additive, such as L-carnitine.

[037] As used herein, the term "antioxidant" is recognized in the art and refers to synthetic or natural substances that prevent or delay the oxidative deterioration of a compound. Exemplary antioxidants include tocopherols, flavonoids, catechins, superoxide dismutase, lecithin, gamma oryzanol; vitamins, such as vitamins A, C (ascorbic acid) and E and beta-carotene; natural components such as camosol, carnosic acid and rosmanol found in rosemary and hawthorn extract, proanthocyanidins such as those found in grapeseed or pine bark extract, and green tea extract.

[038] The term "flavonoid" as used herein is recognized in the art and is intended to include those plant pigments found in many foods that are thought to help protect the body from cancer. These include, for example, epi-gallo catechin gallate (EGCG), epi-gallo catechin (EGC) and epi-catechin (EC).

[039] Any dosage form, and combinations thereof, are contemplated by the present invention. Examples of such dosage forms include, without limitation, chewable tablets, elixirs, liquids, solutions, suspensions, emulsions, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, suppositories, creams, topicals, ingestibles, injectables, infusions, health bars, confections, animal feeds, cereals, cereal coatings, and combinations thereof. The preparation of the above dosage forms are well known to persons of ordinary skill in the art.

[040] For example, health bars can be prepared, without limitation, by mixing the formulation plus excipients (e.g., binders, fillers, flavors, colors, etc.) to a plastic mass consistency. The mass is then either extended or molded to form "candy bar" shapes that are then dried or allowed to solidify to form the final product.

[041] Soft gel or soft gelatin capsules can be prepared, for example, without limitation, by dispersing the formulation in an appropriate vehicle (e.g. rice bran oil, monoterpene and/or beeswax) to form a high viscosity mixture. This mixture is then encapsulated with a gelatin based film using technology and

machinery known to those in the soft gel industry. The industrial units so formed are then dried to constant weight. Typically, the weight of the capsule is between about 100 to about 2500 milligrams and in particular weigh between about 1500 and about 1900 milligrams, and more specifically can weigh between about 1500 and about 2000 milligrams.

[042] For example, when preparing soft gelatin shells, the shell can include between about 20 to 70 percent gelatin, generally a plasticizer and about 5 to about 60% by weight sorbitol. The filling of the soft gelatin capsule is liquid (principally limonene, in combination with rice bran oil and/or beeswax if desired) and can include, apart from the antioxidant actives, a hydrophilic matrix. The hydrophilic matrix, if present, is a polyethylene glycol having an average molecular weight of from about 200 to 1000. Further ingredients are optionally thickening agents. In one embodiment, the hydrophilic matrix includes polyethylene glycol having an average molecular weight of from about 200 to 1000, 5 to 15% glycerol, and 5 to 15% by weight of water. The polyethylene glycol can also be mixed with propylene glycol and/or propylene carbonate.

[043] In another embodiment, the soft gel capsule is prepared from gelatin, glycerine, water and various additives. Typically, the percentage (by weight) of the gelatin is between about 30 and about 50 weight percent, in particular between about 35 and about weight percent and more specifically about 42 weight percent. The formulation includes between about 15 and about 25 weight percent glycerine, more particularly between about 17 and about 23 weight percent and more specifically about 20 weight percent glycerine.

[044] The remaining portion of the capsule is typically water. The amount varies from between about 25 weight percent and about 40 weight percent, more particularly between about 30 and about 35 weight percent, and more specifically about 35 weight percent. The remainder of the capsule can vary, generally, between about 2 and about 10 weight percent composed of a flavoring agent(s), sugar, coloring agent(s), etc. or combination thereof. After the capsule

is processed, the water content of the final capsule is often between about 5 and about 10 weight percent, more particularly 7 and about 12 weight percent, and more specifically between about 9 and about 10 weight percent.

5 **[045]** As for the manufacturing, it is contemplated that standard soft shell gelatin capsule manufacturing techniques can be used to prepare the soft-shell product. Examples of useful manufacturing techniques are the plate process, the rotary die process pioneered by R. P. Scherer, the process using the Norton capsule machine, and the Accogel machine and process developed by Lederle. Each of these processes are mature technologies and are all widely available to

10 any one wishing to prepare soft gelatin capsules.
[046] Typically, when a soft gel capsule is prepared, the total weight is between about 250 milligrams and about 2.5 gram in weight, e.g., 400-750 milligrams. Therefore, the total weight of additives, such as vitamins and antioxidants, is between about 80 milligrams and about 2000 milligrams,

15 alternatively, between about 100 milligrams and about 1500 milligrams, and in particular between about 120 milligrams and about 1200 milligrams.
[047] For example, a soft gel capsule can be prepared by mixing a 35% solution of CoQ-10 and limonene (w/w) (e.g., 104 milligrams of CoQ-10 in 193.14 milligrams of limonene) with between about 0.01 grams and about 0.4

20 grams (e.g., 0.1 grams) tocopherol, between about 200 grams and about 250 grams (e.g., 225 grams) rice bran oil and between about 0.01 grams and about 0.5 grams betacarotene (e.g. about 0.02 grams). The mixture is then combined with encapsulated within a gelatin capsule as described above.
[048] The present invention also provides packaged formulations of a

25 monoterpene with CoQ-10 and instructions for use of the tablet, capsule, elixir, etc. Typically, the packaged formulation, in whatever form, is administered to an individual in need thereof that requires and increase in the amount of CoQ-10 in the individual's diet. Typically, the dosage requirements is between about 1 to about 4 dosages a day.

5 [049] CoQ-10 has been implicated in various biochemical pathways and is suitable for the treatment of cardiovascular conditions, such as those associated with, for example, statin drugs that effect the body's ability to product coQ-10 naturally. CoQ-10 has also been implicated in various periodontal diseases. Furthermore, CoQ-10 has been implicated in mitochondrial related diseases and disorders, such as the inability to product acetyl coenzyme A, neurological disorders, for example, such as Parkinson's disease and, Prater-Willey syndrome.

10 [050] The following examples are intended to be illustrative only and should not be considered limiting.

[051] **Examples**

15 [052] Formulations of CoQ-10 can be prepared in the following ratios by mixing the components together and then placing into a soft gel capsule.

	<u>Component</u>	<u>Example 1</u>	<u>Example 2</u>
	CoQ-10	104.09 mg	104.09 mg
	Mixed Tocopherols	269.03 mg	269.03 mg
	(372 IU/g)		
20	Rice Bran Oil	176.02 mg	-----
	Natural Beta Carotene	10.05 mg	10.05 mg
	(20% by weight)		
	Yellow Beeswax	20.0 mg	-----
	D-limonene	-----	196.02 mg
25	Total weight	580 mg	580 mg

[053] Example 2 demonstrates that the use of limonene solubilizes CoQ-10 without the requirement of beeswax and/or rice bran oil being present.

Examples 1 and 2 could be incorporated into soft gel capsules by standard methods known in the art.

	<u>Component</u>	<u>Example 3</u>	<u>Example 4</u>
5	CoQ-10	17.95 g	17.95 g
	EPAX 2050TG	48.77 g	45.49 g
	D-Limonene	35.70 g	35.70 g
	5-67 Tocopherol (1000 IU/g)	-----	0.86 g

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[054] Examples 3 and 4 demonstrate that CoQ-10 can be solubilized in scalable quantities. Additives, such as EPAX 2050 TG (an ω -3 oil; 20% EPA/50% DHA as triglycerides, remainder fatty acid/triglycerides; Pronova Biocare) and tocopherols (5-67 Tocopherol; BD Industries) can easily be incorporated into such limonene containing formulations. The resultant mixtures contained approximately 100 mg of CoQ-10 per soft gel capsule. Preparation of the soft gel capsules was accomplished by methods well known in the art.

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[055] Although the present invention has been described with reference to preferred embodiments, persons skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

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[056] All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.